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TOWNSEND and TOWNSEND and CREW LLP

By: Karen Karlin

PATENT
Atty. Docket No.: 018512-002211US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Examiner: Olga N. Chernyshev
Timothy J. JEGLA	Art Unit: 1646
Application No.: 09/767,597	APPELLANT'S REPLY BRIEF UNDER 37 C.F.R. 1.193(b)(1)
Filed: January 22, 2001	
For: HUMAN HAC3	

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Sir:

This brief is filed in triplicate pursuant to 37 C.F.R. §1.193(b)(1), in response to the Examiner's Answer ("the Answer"), mailed September 9, 2003. A request for an oral hearing pursuant to 37 C.F.R. §1.194 is filed herewith as a separate paper.

The present invention relates to a novel subunit of a hyperpolarization-activated cation channel (HAC as acronym), which is termed HAC3 and primarily expressed in the central nervous system (CNS). The instant application asserts a specific

and substantial utility of the invention: the identification of HAC3 ion channels subunits allows the identification of modulators of hyperpolarization-activated cation channels comprising a HAC3 subunit, which modulators are useful for treating disorders related to abnormal cell excitability, *e.g.*, migraine and seizure. The Examiner has taken the position that the asserted utility is not credible.

In the Answer, the utility rejection and enablement rejection based on lack of utility are maintained. Specifically, the Examiner states that the present case is analogous to *Brenner v. Manson*, 148 USPQ 689 (Sup. Ct. 1966), and that a holding of lack of utility required by 35 U.S.C. §101 is thus appropriate.

Appellants disagree. In *Brenner*, the Court held that the invention has no patentable utility because the claimed chemical process produces a steroid that has no known use and is only structurally similar to a compound with tumor-inhibiting effects. The present invention cannot be analogized to the one in *Brenner*. As asserted in the present application, HAC3 channels belong to a class of hyperpolarization-activated cation channels capable of mediating neuronal excitability. The modulators of HAC3 channels are useful for treating disorders caused by altered CNS excitability. The claimed cation channels thus have been assigned a definite physiological function (modulating CNS excitability), and associated with specific diseases (migraine, epilepsy, etc.), and can be used for the purpose of treating the diseases. These assertion are supported by both subjective reasons, *e.g.*, structural features and electrophysiological characteristics of HAC3, as well as objective reasons, *e.g.*, the opinions of those ordinarily skilled in the pertinent art, as evidenced by Dr. Neil Castle's Declaration and the Pape *et al.* reference (both made of record June 10, 2002).

In contrast to the above, the *Brenner* case presents a very different situation. The activities of the steroid produced by the claimed process in *Brenner* are far more unpredictable in nature, due to the high level of unpredictability in the science of steroid chemistry. In *Brenner*, there was no evidence other than structural homology to

support the purported anti-tumor activity of the steroid. Yet, the view apparently held by skilled artisans in the field was that "minor changes in the structure of a steroid may produce profound changes in its biological activity." *Id*, 694, footnote 19, quoting a prior art reference made of record in *Brenner*. The party seeking a holding of sufficient utility in *Brenner* thus failed to establish a reasonable likelihood of the asserted anti-tumor activity. Appellants therefore submit that the present case and *Brenner* are factually dissimilar and the Court's holding of insufficient utility in *Brenner* cannot be applied mechanically to the present application.

The Examiner further points to a particular sentence found in the instant specification, "[i]solation of human HAC3 is therefore desirable, to better understand the physiology of HAC3 in humans and for the development of therapeutic and diagnostic applications to diseases related to hHAC3 in humans," and uses this language to support her notion that the invention is not complete and the asserted utility is not established (bridging paragraph between pages 4 and 5 of the Answer).

The Examiner's reliance on this sentence is misplaced, because this sentence is not Appellants' utility statement. The particular manner of describing the claimed invention in this sentence merely reflects the fact that the full physiological functions of HAC3 remain a subject of future studies. This fact does not affect, let alone negate, the credibility of Appellants' asserted utility. This quoted statement about gaining better understanding is generally applicable to any protein, because even with a protein that has been thoroughly studied and well characterized, there is always more study that can be done "to better understand" the protein's physiological significance. On the other hand, the lack of complete understanding regarding the exact manner of function does not preclude a finding of sufficient utility. In fact, there are plenty of examples where a patented therapeutic agent is proven effective for its claimed use, yet the mechanism of its action is not fully illustrated and remains under continued investigation.

In contrast to the Examiner's quote of the specification, Appellants' asserted utility is presented, *e.g.*, on page 8, line 20, to page 9, line 8, of the specification, which states that HAC3 is a subunit of a hyperpolarization-activated cation channel and can be used for identifying modulators of such cation channels, and that the modulators are useful for treating disorders involving abnormal ion influx (such as migraine and seizure). The Examiner does not dispute Appellants' assertion that HAC3 is a subunit of a hyperpolarization-activated cation channel and can modulate neuronal excitability. Neither do Appellants dispute the Examiner's assertion that there are a "plurality of ion channels" involved in a "broad range of functions." Therefore, the sole point of disagreement is whether one of skill in the art would believe Appellants' assertion that HAC3 channels can be used to as therapeutic targets for treating specific disorders caused by abnormal cell excitability (such as migraine and seizure), in light of the expression pattern and electrophysiolgical characteristics of HAC3 channels disclosed by the present application, as well as the general knowledge available to a person of ordinary skill in the art.

According to MPEP §2107.02 III A, an assertion of utility creates a presumption of utility sufficient for the patentability requirement under 35 U.S.C. §101. To overcome this presumption, it is insufficient to merely question the asserted operability-- the Examiner must carry the initial burden to make a *prima facie* showing of lack of utility by setting forth factual reasons why one of skill in the art would not believe the asserted operability. *In re Gauber*, 187 USPQ 664, 666 (CCPA 1975).

The only factual reason the Examiner has so far provided to support her position is the number of ion channels expressed in CNS and their diverse physiological functions. Yet this fact does not prove the link impossible or even unlikely between HAC3 channels and specific diseases such as migraine and epilepsy. In the Answer as well as in the previous Office Actions, the Examiner repeatedly emphasizes that Appellants have not proven the connection between HAC3 and cell excitability-related disorders. *See, e.g.*, "[t]he instant specification fails to provide any specific reasoning or

evidence of record, which would associate the instant polypeptide with any dysfunction or disorder" (page 6 lines 6-8 of the Answer); "there is no disclosure [in the specification] that the claimed polypeptides are specifically associated with migraine and seizure" (page 8 lines 10-11 of the Answer); "[t]here is no evidence of record showing that the new[ly] cloned cation channel is associated with any specific biological process.....Nor is it shown that it is associated with known compounds, specific effects or known disorders or diseases" (page 8 line 21 to page 9 line 2 of the Answer). These statements reflect the incorrect standard the Examiner has applied in assessing utility, which erroneously places the initial burden of proof on an applicant instead of an examiner.

The Examiner apparently also relied on the same improper standard when considering Dr. Castle's Declaration, as the Examiner states, "the Declaration, as well as the instant specification, fails to clearly identify the specific connection between HAC3 polypeptides and migraine or epilepsy" (page 10, lines18-20, of the Answer). As discussed above, Appellants need not carry the initial burden to prove the assertion that HAC3 can be used as a target for treating disorders associated with aberrant CNS excitability; it is the Examiner who must carry the initial burden to disprove this assertion. The Examiner has not done that.

Even if the Examiner's standard for assessing utility were correct, and even if the plurality of ion channels expressed in CNS and their diverse functions would be regarded as sufficient factual reasons to dispute the asserted connection between HAC3 and hyperexcitability-related conditions and thus properly support a *prima facie* case of lack of utility, Appellants submit that the Examiner's argument would have to be considered together with Dr. Castle's Declaration. According to the Federal Circuit, the Examiner bears the initial burden of presenting a *prima facie* case of unpatentability. If this initial burden is met, the burden of coming forth with evidence or argument then shifts to the applicant. "After the evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of

evidence with due consideration to persuasiveness of argument." *In re Oetiker*, 24 USPQ2d 1443 at 1444 (Fed. Cir. 1992).

In the present case, Dr. Castle attests in the Declaration that one of skill in the art "would readily recognize Hac3 as a useful target for the treatment of diseases and conditions caused by altered neuronal or cell excitability, " and "would expect blockers of Hac3 to decrease overall CNS activity" and to "have utility for the treatment of diseases of hyperexcitability, such as epilepsy and migraine" (paragraph 8 of the Declaration). Furthermore, Dr. Castle states that HAC3 modulators may be useful therapeutic agents even if HAC3 is not the direct cause of these conditions (paragraph 10 of the Declaration).

The essence of Dr. Castle's statements is that HAC3 modulators can be used for treating disorders related to abnormal neuronal excitability, because HAC3 is one of the ion channels that can regulate CNS cell excitability and not necessarily because altered HAC3 function is the direct cause of these disorders. Dr. Castle's Declaration presents an objective truth that directly rebuts the Examiner's conclusion that an artisan would not believe the asserted connection between HAC3 and cell excitability-associated diseases such as migraine and thus would not believe the asserted utility. When the Examiner's argument and Dr. Castle's Declaration are considered together, Appellants submit that the Examiner has failed to prove, by a preponderance of evidence, that the instant invention has no specific and substantial credible asserted utility.

The Examiner also takes the position that the asserted utility of the present invention is not specific, because "a plurality of ion channels.....can mediate cell excitability" (page 12 lines 8-9 of the Answer). Appellants cannot agree with the reasoning, because the Examiner merely states an irrelevant truth. While it is true that more than one ion channels might be involved in mediating CNS cell excitability, this fact does not lead to the conclusion that using modulators of HAC3, one of these channels, to treat CNS hyperexcitability diseases is not a specific utility.

According to the Pape reference, there is a class of hyperpolarization-activated cation channels involved in mediating neuronal excitability. It is possible that modulators of one HAC channel may also modulate other members of the class. Even though such modulators (and thus their use for treating diseases) may not be specific for an individual HAC channel (such as HAC3), they are still specific for the class of HAC channels, because these HAC modulators cannot modulate the activity of other ion channels that do not belong to this class (such as ion channels activated not by hyperpolarization but by various ligands). As such, Appellants contend that the asserted use of HAC3 for identification of its modulators as potential therapeutic agents is a specific utility for the claimed HAC3 ion channels and not just any ion channels.

The Examiner further argues that the claimed utility is not substantial, because "the instant specification does not disclose the identity of the signal or a specific physiological pathway in the connection with any process which one would wish to manipulate for a desired clinical effect, screening for agonists or antagonists of the pathway through which that ion channel transduces its signal in response to that signal is not particularly useful" (the paragraph bridging pages 12 and 13 of the Answer). Appellants reiterate that the asserted utility, *i.e.*, treatment of specific diseases such as migraine, is a substantial and practical "real-world use." The use of HAC3 modulators to successfully treat these diseases does not require the identification of the precise signal or physiological pathway through which HAC3 channels are linked to these diseases.

Appellants also disagree with the Examiner's analysis of the fact pattern of the present case in comparison with Example 8 of the Revised Interim Utility Guidelines Training Materials ("the Guidelines"). According to the Examiner, a specific and substantial credible utility is found for compound A, which inhibits enzyme XYZ, because XYZ "has a substrate specificity, which defines its unique biological function"; whereas HAC3's function--modulating CNS cell excitability or modulating the passage of ions under various conditions--is not a unique characteristics but rather universal to a live cell, a modulator for HAC3 has thus no utility under 35 U.S.C. §101. This analysis

is flawed. As discussed above, only certain ion channels are responsible for regulating CNS excitability. This regulatory function is thus specific for the class of ion channels. Even within the class of HAC channels where more than one channel can modulate cell excitability and modulate ion passage in response to various conditions, a HAC3 channel has its own distinct molecular makeup and electrophysiological characteristics (see Example I on pages 62-64 of the specification), which to one skilled artisan are just as unique as the substrate specificity of enzyme XYZ. The Examiner's distinction of the present case from Example 8 of the Guidelines is thus improper.

The Examiner goes on to analogize the fact pattern of the instant invention with Example 12 of the Guidelines in an attempt to buttress the conclusion of lack of patentable utility. Example 12 describes an receptor protein that is held to lack utility, because the protein's biological function or its associated disease or body condition has not been identified, nor has the function of protein's ligand been identified. This example is rather different from the present case. The instant specification discloses the biological function of HAC3, *e.g.*, modulating CNS cellular excitability, which the Examiner does not dispute. The instant specification also discloses the conditions that can be treated by HAC3 modulators, *e.g.*, disorders caused by hyperexcitability such as migraine or epilepsy, which is supported by Dr. Castle's Declaration. Appellants thus submit that Example 12 does not support the conclusion of lack of patentable utility in the present case due to significant factual differences.

Appellants in addition wish to traverse the Examiner's opinion on the present case in connection with the discussion about *Nelson v. Bowler*, 206 USPQ 881 (CCPA 1980). On page 15 of the Answer, the Examiner states, "[i]n the instant case, assertions the '[b]ecause abnormal ion influx and altered cell excitability cause various diseases and disorders, compounds capable of modulating ion channels, such as hyperpolarization-activated ion channels, are useful as therapeutic agents for treating these conditions' (page 14, first paragraph of the brief) clearly establish that the instant invention cannot be used 'in a manner which provides some immediate benefit to the

public.'" The paragraph quoted from the Appeal Brief simply does not support the Examiner's conclusion of no "immediate benefit," as therapeutic agents for treating diseases and disorders caused by abnormal ion influx and altered cell excitability are most certainly capable of providing "immediate benefit to the public."

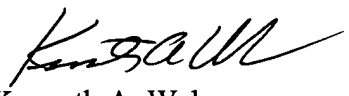
Moreover, the Examiner states that the "isolated naturally occurring human protein [HAC3].....is not readily usable in its current form" (page 15 line 15 of the Answer). This assertion is incorrect. As attested by Dr. Castle in his Declaration, because the present application provides HAC3 coding sequence and polypeptide, "the skilled practitioner can routinely identify agonists or antagonists of a Hac3 channel useful for modulating neuronal excitability in the cell and in controlling CNS diseases related CNS excitability" (paragraph 6 of the Declaration). The claimed invention is thus "readily usable in its currently form."

Finally, Appellants take the opportunity to restate that the Examiner has improperly imposed an elevated utility standard that requires a direct causal connection to be established between a newly identified protein and specific diseases. This heightened utility standard is inconsistent with the prevailing case law, where the illustration of mechanism is never a part of the utility requirement. This heightened standard is also contrary to sound public policy, which encourages early disclosure of useful new inventions. If, before patent protection can be granted, a patent applicant is required to establish the exact mechanism how a newly identified protein exerts its physiological function despite fully effective uses of this protein, the disclosure of many exciting new discoveries will be greatly delayed.

In summary, Appellants submit that the utility rejection is improper because improper standard has applied to assess the utility of the present invention. The withdrawal of the utility rejection is therefore respectfully requested. Consequently, the enablement rejection based on lack of utility is also improper and should be withdrawn as well.

In view of the foregoing, Appellant believes all claims now pending in this Application are in condition for allowance.

Respectfully submitted,



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